

Review article: novel oral-targeted therapies in inflammatory bowel disease

Ghosh, Subrata; Iacucci, Marietta

DOI:
[10.1111/apt.14669](https://doi.org/10.1111/apt.14669)

License:
None: All rights reserved

Document Version
Peer reviewed version

Citation for published version (Harvard):
Ghosh, S & Iacucci, M 2018, 'Review article: novel oral-targeted therapies in inflammatory bowel disease', *Alimentary Pharmacology & Therapeutics*. <https://doi.org/10.1111/apt.14669>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Checked for eligibility: 05/06/2018
This is the peer reviewed version of the following article: White JR, Phillips F, Monaghan T, et al. Review article: novel oral-targeted therapies in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2018;47:1610–1622., which has been published in final form at <https://doi.org/10.1111/apt.14669>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

NOVEL ORAL TARGETED THERAPIES IN INFLAMMATORY BOWEL DISEASE

Jonathan R White¹, Frank Phillips¹, Tanya Monaghan¹, Waleed Fateen¹, Sunil Samuel¹, Subrata Ghosh², Gordon W Moran¹

¹ NIHR Biomedical Research Centre in Gastrointestinal and Liver Diseases at Nottingham University Hospitals NHS Trust and The University of Nottingham, NG7 2UH, Nottingham, United Kingdom

² NIHR Biomedical Research Centre, Institute of Translational Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, United Kingdom

Summary

Background

There is a great unmet clinical need for efficacious, tolerable, economical and orally administered drugs for the treatment of inflammatory bowel disease (IBD). New therapeutic avenues have become possible including the development of medications that target specific genetic pathways found to be relevant in other immune mediated diseases.

Aims

To provide an overview of recent clinical trials for new generation oral targeted medications that may have a future role in IBD management.

Methods

Pubmed and Medline searches were performed up to 01/03/18 using keywords: 'IBD', 'UC', 'CD', 'inflammatory bowel disease' 'ulcerative colitis', 'Crohn's disease' in combination with 'phase', 'study', 'trial', and 'oral'. A manual search of the clinical trial register, article reference lists, abstracts from meetings of *Digestive Disease Week*, *United European Gastroenterology Week* and *ECCO congress* were also conducted.

Results

In randomised controlled trials primary efficacy endpoints were met for tofacitinib (JAK 1/3 inhibitor-phase III), upadacitinib (JAK 1 inhibitor-phase II) and AJM-300 (α 4-integrin antagonist-phase II) in ulcerative colitis. Ozanimod (S1P receptor agonist-phase II) also demonstrated clinical remission. For Crohn's disease, filgotinib (JAK1 inhibitor-phase II) met primary endpoints and laquinimod (quinolone-3-carboxide small molecule-phase II) was also efficacious. Trials using mongersen (SMAD7 inhibitor) and vidofludimus (dihydroorotate dehydrogenase inhibitor) have been halted.

Conclusions

This is potentially the start of an exciting new era in which multiple therapeutic options are at the disposal of physicians to treat IBD on an individualised basis. Head-to-head studies with existing treatments and longer term safety data are needed for this to be possible.

Keywords

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, immunotherapy

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic and progressive immune mediated condition of the gastrointestinal (GI) tract influenced by both genetic and environmental factors. Often patients require lifelong medical therapy and others surgery depending on disease severity. A meta-analysis showed the 5 and 10 year risk for needing surgery for Crohn's disease (CD) and ulcerative colitis (UC) was 33.3%, 46.6%, 11.6 and 15.6% respectively (1). Approximately 25% of CD patients will require additional intestinal surgery within five years of their first (2). The risk of requiring surgery after diagnosis has decreased over the past six decades but remains a significant burden (3). This has both financial implications and a

negative impact on a patient's quality of life (4). For a considerable duration, the mainstay of medical treatment for IBD has been the use of steroids for the induction of remission and immunomodulatory drugs such as azathioprine, mercaptopurine and methotrexate to maintain remission (5). However, since 1997 when Targan *et al* reported the first randomised controlled trial (RCT) to show the effectiveness of the anti-tumour necrosis factor (TNF) infliximab, there has been a paradigm shift in IBD management. This has led to the introduction of a number of anti-TNF and other biological agents such as adalimumab, certolizumab, golimumab, ustekinumab and vedolizumab (6-15).

During the course of this disease, many patients are treated with various immunosuppressive medications either due to a lack of efficacy, loss of response or drug intolerance (16). Up to a third of patients treated with anti-TNF therapy are primary non-responders, whilst a significant proportion (10-15% per year) lose response due to antibody formation (immunogenicity failure) (7, 17-19). These biological agents are also associated with significant adverse events, such as opportunistic infections and immune complications (20, 21). Furthermore, these drugs have the added inconvenience of parenteral administration and associated heavy health care costs (22). In a climate where hospital room capacity is limited, the use of novel oral medication could potentially increase capacity and reduce costs associated with drug infusions.

There remains a great unmet clinical need for new efficacious, tolerable, economical and orally administered drugs. As our understanding of the major inflammatory pathways in IBD have evolved, multiple new therapeutic avenues have become possible. These include the development of new oral medications that target specific pathways found to be relevant in other immune mediated diseases. These include inhibition of cytokine cell signalling, lymphocyte influx and mast cell activity, as well as promotion of the activity of inherent

immunosuppressive pathways (23). This review provides an overview of recent clinical trials for new generation oral targeted medications that may have a role in IBD management in the future.

METHODOLOGY

A broad electronic literature search was conducted using Pubmed and Medline up to 1st March 2018 to identify the relevant studies. The following keywords were used 'IBD', 'UC', 'CD', 'inflammatory bowel disease' 'ulcerative colitis', Crohn's disease', in combination with 'phase', 'study', 'trial', and 'oral'. A manual search of the reference list of initially selected articles, abstracts from the yearly meetings of *Digestive Disease Week*, *United European Gastroenterology Week* and *European Crohn's and Colitis congress* up to 1st March 2018 was also conducted. Clinical trial status was checked on <http://www.clinicaltrials.gov> and <http://www.clinicaltrialsregister.eu>. Only articles published in English were reviewed.

POTENTIAL NEW TREATMENTS: ULCERATIVE COLITIS

α4-INTEGRIN ANTAGONIST

Integrins comprise a family of α4β heterodimeric transmembrane receptors that are constitutively expressed on leukocyte surfaces and are activated by pro-inflammatory cytokines released by activated T cells (24). The integrin family consists of at least 24 different forms representing the combination of 18 α subunits and 8 β subunits. The α-subunit determines integrin ligand specificity. The β subunit connects to the cytoskeleton and affects multiple signalling pathways (25). Inhibiting the interactions between adhesion

molecules and lymphocyte integrins has already proved to be a successful therapeutic strategy for the management of IBD (26).

Vedolizumab is a recombinant humanized, anti- $\alpha 4\beta 7$ integrin monoclonal antibody, which has shown efficacy for induction and remission in both UC and CD (14, 27). Natalizumab (Biogen Idec, Massachusetts, United States) an anti- $\alpha 4$ integrin antibody is also effective in IBD (28, 29) and etrolizumab (Roche, Basel, Switzerland) an anti- $\beta 7$ integrin antibody was investigated in a phase II trial which showed this was more likely to lead to clinical remission than placebo in UC (30). Phase III trials are currently being evaluated in IBD (31-33). A more recent development is AJM 300 (Ajinomoto Pharmaceuticals, Tokyo, Japan), an oral $\alpha 4$ -integrin antagonist that acts by inhibiting the binding of lymphocyte integrins to adhesion molecules expressed on inflamed intestinal endothelium (34). The gut specific $\alpha 4\beta 7$ integrin is expressed on lymphocytes in the gut-associated lymphoid tissue, and interacts with mucosal addressin cell adhesion molecule 1 (MAdCAM-1), whilst the non-gut specific $\alpha 4\beta 1$ integrin is expressed on most leukocytes and interacts with vascular cell adhesion molecule 1 (VCAM1) (35).

AJM-300 was evaluated in a multicentre, randomised, double-blind, placebo-controlled, phase II clinical study (36), involving 102 patients with moderately active UC (Mayo scores of 6-10, endoscopic subscores ≥ 2 , and rectal bleeding subscores ≥ 1) and an inadequate response or intolerable side effects to aminosaliclates or corticosteroids. 960mg dose or placebo was used three times a day for 8 weeks. The primary end-point was a clinical response (decrease in Mayo Score ≥ 3 points and a decrease of $\geq 30\%$ from baseline, with a decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of 0 or 1) at 8 weeks. Secondary endpoint was clinical remission (Mayo Clinic score of ≤ 2 and no subscore > 1 and mucosal healing). The latter was defined as endoscopic subscore of ≤ 1 .

AJM-300 was more effective than placebo in delivering clinical response, remission and mucosal healing. Clinical response were 62.7% in AJM-300 group compared to 25.5% in the placebo group, (odds ratio [OR] 5.35; 95% confidence interval [CI]: 2.23-12.82; p= 0 .0002). Clinical remission rates were 23.5% in the AJM300 group and 3.9% in the placebo group (OR 7.81; 95% CI: 1.64-37.24; p=0 .0099). Mucosal healing rates were 58.8% in AJM300 group and 29.4% in placebo group (OR 4.65; 95% CI: 1.81-11.90; p=0 .0014) (36).

AJM300 was well tolerated, with no severe adverse events observed in this treated cohort. Non-significant laboratory test abnormalities were observed in the AJM300 group. One of the most concerning adverse events of $\alpha 4$ integrin blockade is the development of progressive multifocal leukoencephalopathy (PML), which is seen in higher frequency in patients treated with the natalizumab (37). No PML cases were observed in this study though the safety follow-up period in this study was only short-term (36). However, development opportunities for alpha 4 integrin blockers are likely to be limited due to this risk.

A phase III study is planned.

SPHINGOSINE RECEPTOR MODULATOR

Sphingosine 1-phosphate (S1P) is a sphingosine-derived circulating phospholipid that binds to five G-protein-coupled receptors (GPCRs), termed S1P1-5 (38). S1P receptor's function to regulate processes such as migration, adhesion and endocytosis. They also mediate angiogenesis, vascular permeability and trafficking lymphocytes (39, 40). Ozanimod (RPC1063; Celgene, New Jersey, USA) is an oral sphingosine receptor agonist under development for the treatment of UC and multiple sclerosis. Ozanimod stimulation of

S1P1 on lymphocytes results in receptor internalization and a functional antagonism that causes sequestration of lymphocytes in peripheral lymphoid organs and reduction in circulating lymphocytes. In addition, the activation of S1P receptors on endothelial cells tightens the endothelial barrier, further restricting T cell movement into the intestine (41).

Ozanimod was evaluated in a randomised, double-blind, placebo-controlled phase II trial the TOUCHSTONE study (42). 197 patients with moderate-to-severe active UC (Mayo score ≥ 6 and endoscopy subscore ≥ 2) were randomised in approximately 1:1:1 fashion to once daily 1 mg ozanimod (n=67), 0.5 mg ozanimod (n=65) or placebo (n=65) for 8 weeks (the induction phase). The primary endpoint was clinical remission (defined as Mayo score ≤ 2 and no subscore > 1) at week 8. The exploratory secondary end points were clinical response (defined as reduction in Mayo score of ≥ 3 points and $\geq 30\%$ from baseline, with a decrease in the rectal bleeding score of ≥ 1 or a rectal bleeding score ≤ 1) at week 8. Mucosal healing (defined as endoscopy subscore ≤ 1) and other objective markers such as CRP and faecal calprotectin were measured to examine for changes from baseline. Clinical remission was slightly higher in the 1mg group when compared to placebo (16% vs 6%, $p=0.048$). There was no significant difference in the proportion of patients with a clinical response or endoscopic mucosal healing. Ninety one patients completed a 32 week double blind maintenance phase but there was no significant difference between clinical remission, response and mucosal healing. Ozanimod did not show an adequate efficacy signal and the follow up period was too short to fully assess drug safety. Adverse events were comparable in the three groups; one patient developed a sinus bradycardia and first degree AV block leading to discontinuation of the drug and four patients had elevated liver enzymes (42). The long-term follow up of patients involved in the TOUCHSTONE study demonstrated

treatment with ozanimod to be safe, efficacious and well tolerated in patients with moderate-to-severe UC followed up to two years (43).

Initial results of a further phase II trial of 69 patients treated with ozanimod for moderate-to-severe CD demonstrated a clinical improvement by week 4 and endoscopic improvement by week 12 (44, 45). A phase III trial in moderate-to-severe UC (46) and a phase III trial assessing efficacy and safety in UC (47) are currently ongoing.

Etrasimod (APD334; Arena Pharmaceuticals, California, United States) is a similar compound which selectively targets S1P₁, S1P₄ and S1P₅ in in-vitro assays thus also has the potential for immune cell modulation (48). Etrasimod is currently being evaluated in a randomised, parallel phase II study in patients with UC (49, 50). Another S1P receptor target that has completed a phase II study is amiselimod (MT-1303; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) in CD (51). However, the development of amiselimod has recently been discontinued.

PHOSPHODIESTERASE 4 INHIBITOR

Phosphodiesterase 4 (PDE4) is an enzyme responsible for lysis of cyclic adenosine monophosphate (cAMP) in inflammatory cells. Apremilast (CC-10004, Celgene, New Jersey, USA) is an oral small-molecule inhibitor of PDE4 modulating pro- and anti-inflammatory mediators (52). A phase II randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of apremilast has recently completed recruitment. 170 patients with active UC (Mayo score ≥ 6 to ≤ 11 , Mayo endoscopic score of ≥ 2) who have previously failed conventional treatment but were biologic naïve were recruited. Patients were randomised to 60mg/day, 80mg/day or placebo for 12 weeks. The primary endpoint was the proportion

of patients in clinical remission (Mayo score ≤ 2 and no subscore > 1) at 12 weeks. The secondary endpoint was the proportion of patients with clinical response (reduction in Mayo score of ≥ 3 points and $\geq 30\%$ from baseline, with a decrease in the rectal bleeding score of ≥ 1 or a rectal bleeding score ≤ 1) at 12 weeks.

A significant number of patients treated with 60mg/day were in clinical remission when compared to placebo (31.6% vs 13.8%, $p \leq 0.05$). Clinical response was significantly higher in the 80mg/day group when compared with placebo (67.3% vs 46.6%, $p \leq 0.05$). In the 12 week follow up, the 60mg/day dose showed the most efficacy when compared with placebo. There were no new safety reports (53). This phase II study is currently still active: patients will receive a further 40 weeks of treatment with either 60mg/day or 80mg/day of apremilast and be followed up to week 52 (54).

MAPK INHIBITORS

Mitogen-activated protein kinase (MAPK) superfamily plays an essential role in eukaryotic cell regulation to produce pro-inflammatory cytokines. P38 α , JNKs and ERK1/2 have been shown to be significantly activated in the inflamed colonic mucosa of IBD patients (55).

RDP58 (SangStat Medical Corporation, California, USA), also known as delmitide acetate, is a drug that disrupts cell signalling which is responsible for activating p38 MAPK, JNK, and I kappa kinase (IKK) (56). Travis *et al* first evaluated the efficacy, safety and tolerability of RDP58 in a phase II trial (57). Data for two studies was reported for patients with mild-to-moderate UC (Simple Colitis Activity Index (SCCAI) score 4 to 9 and active disease at sigmoidoscopy (Baron Score ≥ 1) within this trial. In the first study, 34 patients were

randomised (2:1) to RDP58 100mg or placebo. In the second study, 93 patients were randomised (1:1:1) to receive RDP58 200mg, RDP 300mg or placebo.

No statistical difference was observed in the primary and secondary endpoints between RDP58 100mg and placebo. In the second study, treatment success was higher with increasing doses: 71% and 72% for the 200mg and the 300mg dose respectively when compared to 43% for placebo ($p = 0.016$). Adverse events were similar between RDP58 300mg and placebo (57). No further clinical trials evaluating RDP58 in UC are planned.

MODIFIED RELEASE PHOSPHATIDYCHOLINE

UC patients have been found to have a low intrinsic phosphatidylcholine content that reduces intestinal mucus barrier function, making it more susceptible to inflammation and ulceration (58, 59). An improved, modified release phosphatidylcholine (LT02; Dr. Falk Pharma GmbH, Freiburg, Germany) and the first oral therapy targeting stabilisation of gut barrier was evaluated in a double blinded, randomised, placebo controlled phase II study. 156 UC patients with an inadequate response to mesalazine, SCCAI ≥ 5 and bloody diarrhoea were treated with placebo, 0.8, 1.6 or 3.2 g of phosphatidylcholine. The primary endpoint was defined as a >3 point drop in SCCAI from baseline to the end of treatment. SCCAI score change for placebo, 0.8g, 1.6g and 3.2g was 33.3%, 44.3% and 51.7% respectively. The 3.2g dose was statistically superior when compared to placebo at 51.7% compared to 33.3% ($p=0.03$). Histological remission for placebo and all phosphatidylcholine doses was 20% compared to 40.5% ($p=0.016$). Phosphatidylcholine was found to be safe (60). However, two phase III trials have since been terminated in 2017 (61, 62): the first trial because it appeared not to induce remission with the reason for termination of the second trial not yet

disclosed. Another phase III trial is still ongoing comparing phosphatidylcholine to placebo and mesalazine for maintenance of remission in UC (63).

OTHER ORAL AGENTS CURRENTLY IN EARLY DEVELOPMENTAL STAGE

Free fatty acids (FFA) act as energy source but also important for metabolic and inflammation regulation. FFA2 receptor and other G protein receptors are activated by FFA. Knockout mice studies suggest FFA2 has important roles in controlling inflammation (64). GLPG0974 (Galapagos NV, Mechelen, Belgium) is a selective antagonist of FFA2 and was shown to be safe and tolerable in healthy subjects (65). A randomised, exploratory, double blind, phase II trial evaluating the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of GLPG0974 in UC has been completed and results are awaited (66).

There are many other potential new agents at varying stage of developments. LYC-30937 (Lycera Corp, Minnesota, United States) is an oral ATPase modulator currently in phase II studies evaluating its use in UC (67, 68). TOP-1288 (Topivert Pharma Ltd, London, England) is a nonselective kinase inhibitor that has recently been evaluated in a rectal solution in UC (69) and now an oral administered phase I study on healthy subjects has recently been completed (70). GSK2982772 (GlaxoSmithKline, Brentford, England) is a RIP1 kinase inhibitor currently being evaluated in a phase II study (71). Rosiglitazone (GlaxoSmithKline, Brentford, England) a PPAR- γ agonist has been shown to be efficacious in mild to moderate ulcerative colitis in a phase II trial (72). A randomised, cross over placebo controlled phase II trial of VB-201 (VBL Therapeutics, Tel Aviv, Israel), a small oxidized phospholipid molecule in UC has recently been completed but as this study did not meet its primary endpoints there are no plans to continue drug development (73). Finally, AVX-470 (Avaxia Biologics,

Massachusetts, United States) is an orally administered anti-TNF agent that seems promising after the completion of a phase I study (74).

POTENTIAL NEW TREATMENTS: CROHN'S DISEASE

QUINOLONE-3 CARBOXIDE

Laquinimod (TV-5600; Teva Pharmaceutical Industries Ltd, Petah Tikva, Israel) is an oral quinolone-3-carboxide small molecule that has shown efficacy in treating multiple sclerosis (MS) (75, 76) and may have a potential role in treating Huntington's disease (77) and lupus nephritis (78). Both animal and *in vitro* experimental studies have alluded to various mechanisms by which this drug interacts with the immune and nervous system in MS. Laquinimod has been shown to decrease pro-inflammatory immune cells and the activation of anti-inflammatory genes. It also exhibits effects on regulatory T cells by promoting their differentiation (79). A study in experimental autoimmune encephalomyelitis (EAE) (an animal model of MS) has found that quinolone-3-carboxamides inhibited the interaction of S100A9 with two receptors, toll-like receptor 4 and receptor of advanced glycation end products, thereby preventing the downstream release of inflammatory cytokines, including tumour necrosis factor α (TNF α) and interleukin (IL)-1 (80). Laquinimod has also been shown to increase levels of the anti-inflammatory cytokines IL-10 and transform growth factor β (TGF β) in both T and B cells, suppressing immune activity and downregulating the immunogenicity of the dendritic cell response (81). Laquinimod treatment has been shown to inhibit the ability of the CCR7-binding chemokine, CCL21, to stimulate very late antigen-4 (VLA-4) adhesiveness to its natural ligand, vascular cell adhesion molecule-1 (VCAM-1) in

splenic T cells isolated from immunized mice (82) and reduce the *in vitro* secretion of several chemokines participating in the recruitment of leucocytes to inflammatory tissue sites (83).

Laquinimod was evaluated in an exploratory phase IIa multicentre, randomised, double blind placebo-controlled and dose-finding trial. 117 patients were randomised to laquinimod doses of 0.5, 1, 1.5 or 2 mg/day, in a 1:1:1:1 fashion, while 63 patients were exposed to placebo for 8 weeks. CDAI scores, CRP, and faecal calprotectin were recorded at week 0, 2, 6, 8 and 12. Treatment failures (TF) were defined as patients who were not responding, needed biologic, immunosuppressive therapy or surgery. Clinical remission was defined as (CDAI <150 and no TF). Endpoints were to assess safety profile, dosing and the number of patients in clinical remission (CDAI <150 and no TF). Other endpoints included the number of patients with a clinical response with a reduction of CDAI score by ≥ 70 & ≥ 100 points from baseline, in remission, no TF and a mean change in objective markers from baseline. Although this study was not powered for efficacy, the lowest dose 0.5mg/day had the highest response rate when compared to placebo. 48% were in remission at the end of week 8 compared to 15.9% in the pooled placebo group. CDAI 70 and 100 were 62% and 55% respectively in the 0.5mg/day group compared with 35% and 32% respectively of patients exposed to placebo. The higher doses showed similar responses to placebo (84).

D'Haens *et al* also investigated whether changes in plasma concentrations could explain the clinical improvement seen in lower doses. Laquinimod concentration reached its maximum within one hour of administration and remained at a steady plasma concentration throughout the 24 hour period. The pharmacokinetics seems to be linear in CD patients in the dose range 0.5-2mg/day. The pharmacokinetics could not explain the improved response at lower dose (85).

Laquinimod could be used safely for 8 weeks at all doses with an adverse event profile similar to placebo. Incidence of adverse events in all doses was 86.2%-96.7% vs placebo 82.5% (84, 85).

Phase IIb/III trials are currently awaited.

ANTISENSE OLIGONUCLEOTIDE SMAD7 INHIBITOR

Reduced tissue growth factor- β receptor type I (TGF- β 1) cytokine activity due to overexpression of SMAD7 is seen in individuals with IBD (86, 87). Mongersen (GED-0301; Celgene, New Jersey, USA) is a new class of drug (86) which acts to reinstate the TGF β 1 immunosuppressive pathway (88).

Mongersen's efficacy and safety was evaluated in a multicentre, randomised, double-blind, placebo-controlled phase II trial involving 166 patients with moderate-to-severe CD (Crohn's Disease Activity Index 220-400). Participants were randomised to receive placebo or daily mongersen for 14 days. Clinical response was significantly higher in the 160mg and 40mg/day groups when compared to placebo (65% and 55% vs 10%, $p < 0.001$ (89). A post-hoc analysis of this trial showed neither an elevated CRP nor duration of disease impacted on efficacy. No association was seen between baseline CDAI and remission rates but the 40mg dose showed the lowest remission rates with CDAI ≥ 260 (90).

However, a significant limitation of the Monteleone *et al* study was that the inclusion criteria were based on CDAI score and with no objective endoscopic measure of disease activity. At baseline, 39% of participants had a normal CRP (91) implying low disease activity in the exposed population, so patients were not reflective of the usual moderate-to-severe

patients. Moreover the primary endpoint was clinical remission only as measured through CDAI and this was only measured at 28 days. As such, no data are available on long-term clinical remission, endoscopic remission or safety.

In a recent noteworthy turn of events, Celgene has recently terminated their Phase III REVOLVE and SUSTAIN clinical trials of mongersen following recommendation from the external Data Monitoring Committee. This decision was based upon the lack of emerging benefit but not safety findings during their recent review of interim unblinded data. The planned Phase III DEFINE study in Crohn's will also not be initiated. However, a phase II trial in UC has recently completed recruitment (92). Celgene is waiting to review the full dataset from this trial for UC to determine the next steps.

POTENTIAL NEW TREATMENTS: CROHN'S DISEASE AND ULCERATIVE COLITIS

JANUS KINASE INHIBITORS

Janus kinases (JAKs) are a family of intracellular protein tyrosine kinases: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). These are crucial to the downstream regulation of inflammatory mediators. Transcription factor STATs (signal transducer and activation of transcription) are activated by the binding of transmembrane receptors. A number of cytokines deliver their function by activating the JAK-STAT pathway thus having an important role in the immune system and development of immune mediated disorders (93, 94). JAK inhibition results in suppression of B and T cells but retains regulatory T cell function, therefore, is an important target in IBD (95, 96).

Tofacitinib

Tofacitinib (CP-690,550; Pfizer, New York City, USA) is a JAK 1 and 3 inhibitor that has been studied in autoimmune conditions, including rheumatoid arthritis and psoriasis with a good overall efficacy and an acceptable safety profile (97-99).

The use of tofacitinib in UC was evaluated in a multi-centre, double-blind, placebo-controlled, dose-ranging phase II study, including 194 adults with moderate-to-severe active UC (Mayo score ≥ 6 and endoscopic subscore ≥ 2) who had failed conventional therapy (100). Stable doses of mesalamine or prednisolone at a maximum of 30mg were permitted during the trial period. Patients were randomised to tofacitinib 0.5, 3, 10, or 15 mg or placebo twice daily for 8 weeks. The primary efficacy end point was a clinical response, defined as an absolute decrease in Mayo score of ≥ 3 points and relative decrease $\geq 30\%$, with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1. Of the secondary end points, clinical remission was defined as Mayo score ≤ 2 with no individual subscore >1 at week 8, endoscopic response was defined as a decrease from baseline in the subscore ≥ 1 at week 8, and endoscopic remission was defined as endoscopy subscore of 0 at week 8. The only statistical significant clinical response was with the 15mg twice a day dose when compared to placebo (78% vs 42%, $p<0.001$). Clinical remission was 13%, 33%, 48%, and 41% at 0.5mg ($p=0.76$), 3mg $p=0.01$, 10 mg ($p<0.001$), and 15 mg ($p<0.001$), respectively when compared with 10% for placebo. Tofacitinib was well tolerated and reasonably effective in moderate-to-severe UC (100). Tofacitinib is also associated with dose-dependent improvement in health related quality of life measures (101). Faecal calprotectin showed a moderate correlation with clinical and endoscopic outcomes in patients receiving tofacitinib. A cut off value of 150 mg/kg showed a fair to good accuracy in classifying these outcomes (102).

Sandborn *et al* recently reported the use of tofacitinib as induction and maintenance therapy in UC. A number of randomised, double blind, placebo controlled phase III trials were conducted. The OCTAVE Induction 1 and 2 trials included patients with moderate-to-severe UC (Mayo score ≥ 6 , endoscopic subscore ≥ 2 and rectal bleeding subscore ≥ 2). Patients with previous treatment failures or unacceptable side effects to anti-TNF or immunomodulatory drugs were included in these studies. Concomitant medications included prednisolone $<25\text{mg/day}$ and oral aminosalicylates. In the first two trials, 598 and 541 patients were randomised (4:1) to induction therapy (10mg twice a day) or placebo for 8 weeks. Primary endpoint of clinical remission (a total Mayo score of ≤ 2 , with no subscore >1 and a rectal bleeding subscore of 0) at 8 weeks was 18.5% in tofacitinib group versus 8.2% in the placebo ($p=0.007$) in the OCTAVE 1 trial. In the OCTAVE 2 trial this was 16.6% versus 3.6% ($p<0.001$). In the OCTAVE 1 trial, the 10mg group mucosal healing rate was 31.3% compared to placebo 15.6% ($p<0.001$). In the OCTAVE 2 trial, this was 28.4% vs 11.6% ($p<0.001$).

Patients who achieved a clinical response (reduction total Mayo score ≥ 3 points, rectal bleeding score ≥ 1 or absolute rectal bleeding subscore of 0 or 1) in the OCTAVE 1 and 2 were eligible to participate in the third OCTAVE Sustain trial. Patients were randomised (1:1:1) to receive 5mg, 10mg or placebo twice a day for 52 weeks. The primary endpoint was remission at 52 weeks. Secondary endpoints were mucosal healing at 52 weeks and sustained steroid free remission (both at 24 and 52 weeks). In this trial clinical remission at 52 weeks were 34.3% in 5mg group, 40.6% in the 10mg group compared with 11.1% in the placebo ($p<0.001$ for both comparisons). Mucosal healing occurred in significantly more patients at 52 weeks. In the 5mg, 10mg and placebo this was 37.4%, 45.7% and 13.1% ($p<0.001$) respectively. Sustained steroid free remission was 34.4%, 47.3% and 5.1%

($p < 0.001$) in the 5mg, 10mg and placebo group respectively. These results demonstrate that tofacitinib is more effective as an induction and maintenance agent than placebo (103). The 3 year interim efficacy and safety data from the OCTAVE 1, 2 and OCTAVE Sustain studies open label long-term extension study reported a similar safety profile to those observed with rheumatoid arthritis patients and a sustained efficacy with 5mg and 10mg twice a day dose (104). Currently one phase I trial (105) and a phase III trial (106) are underway for tofacitinib in UC.

However in patients with CD tofacitinib did not exhibit a significant clinical remission and response rate. The use of tofacitinib in CD was evaluated in a multi-centre, double-blind, placebo-controlled, phase II trial including 139 patients with moderate-to-severe CD (CDAI 220-450). Patients were randomised to (1, 5 or 15 mg twice a day) or placebo for 4 weeks. The primary and secondary endpoints were the proportion of clinical responders at week 4 (CDAI of ≥ 70 points) and clinical remission at 4 weeks (CDAI < 150) respectively. There was no significant difference in the primary and secondary endpoints. It is unclear whether these findings are due to the high placebo response rate or difference in the immunopathology CD and UC (107). Panés *et al* reported a recently conducted phase IIb trial in which CD patients were randomised to 5 mg (n=86), 10 mg twice (n=86) or placebo (n=91) twice a day for 8 weeks. There was no significant difference in remission rates reported despite the longer treatment duration. The clinical response was slightly significantly higher as was CRP reduction in the tofacitinib group when compared to placebo. There was no change in in faecal calprotectin levels (108). Panés *et al* later reported on two randomised, double-blind, placebo-controlled, multicentre phase IIb studies of 180 patients with moderate-to-severe CD. Clinical remission was not significantly different to placebo although there were minor treatment benefits seen in change in biomarkers (secondary endpoints) (109). A number of

factors may have contributed to the high response rate seen in placebo patients. Endoscopy was not centrally read and the severity and extent of ulceration was not defined despite been part of the inclusion criteria. There was also no baseline threshold for objective markers of disease activity. Variation in endoscopic ulceration and inflammatory markers at baseline may have influence the treatment effect of drugs (109, 110).

The most commonly reported adverse events were influenza and nasopharyngitis. Neutropenia has also been reported as well as serious infections such as abscess and pneumonia. There was also a dose-dependent increase in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol which is not completely understood (87, 100, 107).

Filgotinib

Filgotinib (GLPG0634; Galapagos NV, Mechelen, Belgium) is an oral JAK1 inhibitor. Vermeire *et al* evaluated its efficacy and safety in moderate-to-severe CD (CDAI 220-450) with histological evidence of active inflammation in a randomised, double-blind, placebo-controlled phase II study. 174 patients were randomised (3:1) to filgotinib 200 mg once a day or placebo for 10 weeks. Patients were then assigned according to their CDAI clinical responder status to filgotinib 100mg, 200mg or placebo once a day for a further 10 weeks. The primary endpoint was clinical remission (CDAI ≤ 150) at 10 weeks. Secondary endpoints included clinical remission at weeks other than week 10; endoscopic response and clinical response (change from baseline in overall CDAI score and in CDAI component subscores). Clinical response was achieved in 59% in the filgotinib group compared to 41% in placebo ($p=0.453$). Clinical remission was 47% compared to 23% in placebo ($p=0.077$). The safety profile was satisfactory and clinical remission was induced in the filgotinib group. Response

rate was almost twofold higher in patients naïve to anti-TNFs compared to those exposed to at least one. The data suggest that filgotinib could be effective in both anti-TNF naïve and exposed (111). A recent post hoc analysis of this phase II study showed that clinical remission is still seen in CD regardless of disease location and duration (112). Currently phase III trials are underway in CD and UC (113-116).

Upadacitinib

Sanborn *et al* evaluated the safety and efficacy of a JAK 1 inhibitor upadacitinib (ABT-494; AbbVie, Illinois, United States) in CD patients who had inadequate response or intolerant of immunomodulators or anti- TNF therapy in a phase II, multicentre, randomised, double blind placebo controlled trial. This trial included 220 patients with moderate-to-severe CD (CDAI 220-450). Patients were randomised to upadacitinib 3, 6, 12, 24mg twice a day, 24mg once a day or placebo for 16 weeks. Concomitant steroid use was allowed and tapered from week 2. The primary endpoints were clinical remission at week 16 (stool frequency (SF) ≤ 1.5 or abdominal pain (AP) ≤ 1 , and both no worse from baseline) and endoscopic remission at week 12/16 (Simplified Endoscopic Score (SEC) for CD ≤ 4 and ≥ 2 point reduction from baseline, no subscore >1). The overall dose response relationship was also investigated. Significantly more patients achieved clinical remission with 6mg twice a day dose when compared with placebo (27% vs 11% $p \leq 0.05$). There was a significant dose relationship for endoscopic remission when doses 12mg, 24mg twice a day and 24mg once a day compared to placebo (8% $p \leq 0.05$, 22% $p \leq 0.001$, 14% $p \leq 0.01$ and 0% respectively). This study demonstrated both clinical and endoscopic benefit with 6mg doses and above (117, 118). Upadacitinib use also results in a significant and sustainable reduction in markers of inflammation (119). Upadacitinib is also currently being evaluated in phase II trials in UC (120).

Further development

A number of JAK inhibitors are currently in the development phase. A Phase IIb multi-centre randomised, double blind, placebo controlled, parallel group, dose response trial evaluating the safety and efficacy of peficitinib (ASP015K; Astellas Pharma, Tokyo, Japan), a non-selective JAK inhibitor in moderate-to-severe active UC, has recently been completed (121). TD-1473 (Theravance Biopharma, San Francisco, US) a non-selective JAK inhibitor is currently being evaluated in a phase I trial in patients with moderate-to-severe UC (122).

DIHYDROOROTATE DEHYDROGENASE INHIBITOR

Vidofludimus (4SC AG, Martinsried, Germany) is a small molecule which acts by inhibiting activated B and T cells by blocking dihydroorotate dehydrogenase (123). It also inhibits pro-inflammatory cytokines. Herrlinger *et al* conducted a 12 week open label study to evaluate the efficacy, tolerability and safety of vidofludimus in maintaining remission in 34 steroid dependent IBD patients. Despite being relatively safe and well tolerated a further developmental phase II study was discontinued by 4SC in October 2016.(124).

Figure 1, table 1 and 2 summarise molecular targets and drug trial results.

CONCLUSION

For UC, significant treatment benefits have been seen with AJM-300, tofacitinib, and upadacitinib. Ozanimod showed some treatment benefit but the majority of endpoints were not statistically significant. All agents have a favourable short-term safety profile, with the

exception of risk of development of PML with the $\alpha 4$ integrin blockade of AJM-300. Phase III trials are either being planned or are underway for each to gain more data.

For CD, treatment benefits were seen with laquinimod, and phase III trials are underway.

However, there is no apparent benefit with tofacitinib treatment, although the short study duration may have impacted on this. Although the phase II study of filgotinib did not show any statistically significant benefit, phase III studies for both CD and UC are currently active.

Successful phase II but failed phase III trials, such as the mongersen trial, may have been due to high placebo response rates which are unpredictable. This could potentially be largely rectified by introducing endoscopy disease activity in the entry criteria and the use of patient reported outcomes (PRO) as outcome measures of efficacy rather than the older disease activity indices. Failed phase III after successful phase II is not very common but some examples of previous failed therapy were the Anti-IL17A cytokine therapy which was likely due to a mechanistic failure and IL10 due to dosing and drug delivery (125, 126).

Other weakness with a number of the CD trials is that they do not assess mucosal healing at endoscopy which is a desirable treatment goal that leads to increased rates of clinical remission, reduced hospitalization and surgery rates (127). Other weaknesses include low CRP at inclusion, no centrally read endoscopy, short follow up period and a lack of forced steroid tapering dosage. Rectifying these weaknesses is likely to give a true reflection of the difference between the trial agents and placebo, therefore, potentially enabling better design and success at phase III.

Novel oral targeted therapies offer exciting new avenues of treatment for IBD by targeting different parts of the inflammatory cascade. However, for targeted therapy to be achievable, a better understanding of the mechanisms leading to disease development is

crucial. A combination of increased genetic information and biomarker development is required to achieve this. New oral therapies have the potential to provide a more acceptable, convenient treatment on an individualised basis. This may allow for the introduction of more targeted immunosuppression thus reducing inflammation, disease progression and associated complications which ultimately lead to an improved quality of life. Moreover, a better understanding of the disease pathogenesis might allow a strategy to combine targeted therapies hence ultimately achieving the holy grail of truly personalising therapies in IBD.

However, long term infection and malignancy rates also need to be better determined in large prospective studies in addition to side effects, hospital admission rates and other significant costs. There is a growing need for long phase IV studies for these drugs in development and the use of registries like TREAT and PIANO to assess the long-term safety of these drugs. Potentially, the development of more targeted therapies may also mean that complications can be avoided in susceptible individuals compared to the current blanket approach to treatment.

At present, the majority of IBD patients respond to some form of current therapy but the loss of response is a problem. Although population-based studies are suggesting a decrease in surgical rates for both CD and UC (3, 128), better and more targeted therapies are needed to sustain this paradigm shift world-wide. There is presently no head-to-head comparison between presently licenced therapies and future targeted therapies to allow a better understanding of when these targeted therapies should be introduced in present treatment algorithms.

Moreover, there are no clear predictive biomarkers to identify the subgroups of IBD patients that will respond to these new targeted therapies. If these agents are successful, then this will lead to an exciting new era of personalised and precise therapy in IBD, as is already the case in other areas of medicine.

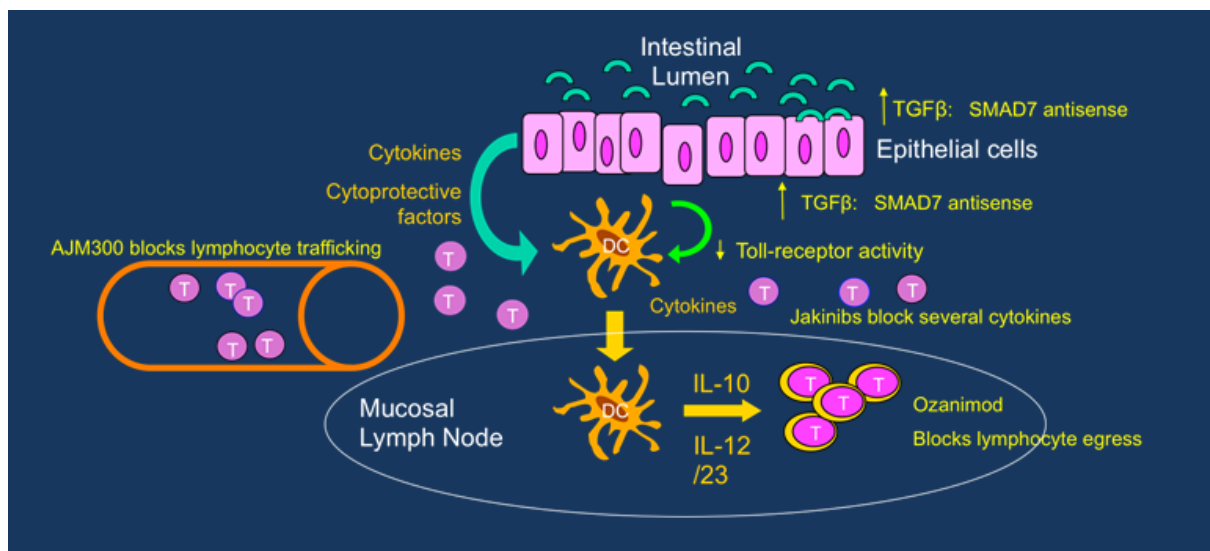


Figure 1: Summary of oral drugs and targets

Drug mechanisms and cellular targets. T= T lymphocytes, DC=Dendritic cells, IL=Interleukin, TGFβ= Tissue growth factor-β receptor.

Table 1: Summary of trials in ulcerative colitis

| Drug trial | Clinical response* | Clinical remission** | Summary and safety |
|--|---|---|--|
| Tofacitinib <i>Janus kinase 1 and 3 inhibitor</i> <i>N= 194</i> <i>Phase II</i> | <ul style="list-style-type: none"> Placebo 42% 0.5 mg 32% 3 mg 48% 10 mg 61% 15 mg 78% <p>(p<0.001)</p> | <ul style="list-style-type: none"> Placebo 10% 0.5 mg 13% (p=0.76) 3 mg 33% (p=0.01) 10 mg 48% (p<0.001) 15 mg 41% (p<0.001) | Dose-related treatment benefit with no severe adverse effects. |
| AJM-300 <i>Anti α4-integrin</i> <i>N=102</i> <i>Phase II</i> | <ul style="list-style-type: none"> Placebo 25.5% 960 mg tds 62.7% <p>(p=0.0002)</p> | <ul style="list-style-type: none"> Placebo 3.9% 960 mg tds 23.5% <p>(p=0.0099)</p> | Significant treatment benefit with no severe adverse events |
| Ozanimod <i>S1P receptor agonist</i> <i>N= 197</i> <i>Phase II</i> | <ul style="list-style-type: none"> Placebo 37% 0.5 mg 54% 1.0 mg 57% <p>p=ns</p> | <ul style="list-style-type: none"> Placebo 6% 0.5 mg 14% 1.0 mg 16% (p=0.048). | Dose-related treatment benefit with no severe adverse effects. Mild elevation in transaminases seen in minority. |
| Apremilast <i>Phosphodiesterase 4 inhibitor</i> <i>N=170</i> <i>Phase II</i> | <ul style="list-style-type: none"> Placebo 46.7% 60mg/day 61.4% 80mg/day 67.3% <p>(p≤0.05)</p> | <ul style="list-style-type: none"> Placebo 13.8% 60mg/day 31.6% (p≤0.05) 80mg/day 21.8% | Treatment benefit at 12 weeks with no new safety concerns |
| Phosphatidylcholine <i>Modified release phosphatidylcholine</i> <i>N=156</i> <i>Phase II</i> | <ul style="list-style-type: none"> Placebo 60% 0.8g/day 77.5% 1.6g/day 73.2% 3.2g/day 82.9% <p>(p=0.03)</p> | <ul style="list-style-type: none"> Placebo 15% 0.8g/day 27.5% 1.6g/day 22% 3.2g/day 31.4% (p=0.09) | Improvement in disease activity and acceptable safety Two phase 3 studies have been discontinued, one ongoing |

**Clinical response: absolute decrease in Mayo score of ≥ 3 points and relative decrease $\geq 30\%$, with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1, at week 8. LT-02: SCCAI decrease ≥ 2 .*

***Clinical remission: Mayo score ≤ 2 with no individual subscore >1 at week 8. LT-02: < 3 mean SCCAI and "blood in stool" subscore of 0.*

tds= three times a day

ns= non-significant

Table 2: Summary of trials in Crohn's Disease

| Drug trial | Clinical response* | Clinical remission** | Summary and safety |
|---|---|---|--|
| Laquinimod <i>quinolone-3-carboxide small molecule</i> <i>N=117</i> <i>Phase IIa</i> | <ul style="list-style-type: none"> Placebo 31.7% 0.5 mg/day 55.2% 1.0 mg/day 40% 1.5 mg/day 27.6% 2.0 mg/day 27.6% <p>p=ns</p> | <ul style="list-style-type: none"> Placebo 15.9% 0.5 mg/day 48.3% 1.0 mg/day 26.7% 1.5 mg/day 13.8% 2.0 mg/day 17.2% <p>p=ns</p> | Treatment benefit seen for 0.5mg dose, with safety profile similar to placebo. Phase IIb/III trials awaited. |
| Filgotinib <i>JAK1 inhibitor</i> <i>N=174</i> <i>Phase II</i> | <ul style="list-style-type: none"> Placebo 41% 200mg/day 59% <p>(p=0.0453)</p> | <ul style="list-style-type: none"> Placebo 23% 200mg/day 47% <p>(p=0.0077)</p> | Induces remission in CD. Acceptable safety profile |
| Upadacitinib <i>JAK1 inhibitor</i> <i>N=220</i> <i>Phase II</i> | <ul style="list-style-type: none"> Placebo 32% *** 12mg/day 57% <p>p≤0.01</p> <ul style="list-style-type: none"> 48mg/day 61% <p>p≤0.01</p> | <ul style="list-style-type: none"> Placebo 11% **** 12mg/day 27% <p>p≤0.05</p> | Induces remission in CD in doses 12mg/day and higher. Acceptable safety profile |
| Mongersen <i>Antisense oligonucleotide</i> <i>SMAD7 inhibitor</i> <i>N=166</i> <i>Phase II</i> | <ul style="list-style-type: none"> Placebo 17% 10 mg/day 37% <p>(p=0.04)</p> <ul style="list-style-type: none"> 40 mg/day 58% <p>(p<0.001)</p> <ul style="list-style-type: none"> 160 mg/day 72% <p>(p<0.001)</p> | <ul style="list-style-type: none"> Placebo 10% 10mg/day 12% 40mg/day 55% 160mg/day 65% <p>(p<0.001)</p> | <p>Significant dose-related treatment benefit that is sustained, with safety profile similar to placebo.</p> <p>Phase 3 studies have been discontinued</p> <p>Phase II trial in UC completed recruitment</p> |

*Clinical response: reduction of CDAI by >100 points by day 28. Filgotimib: change from baseline in overall CDAI score and in CDAI component subscores.

** Clinical remission: reduction of CDAI by >150 after 2 week and maintained for > 2 week. Filgotimib trial used CDAI ≤150 at 10 weeks.

****Clinical response ($\geq 30\%$ reduction from baseline in AP or SF with neither worse than baseline)*

****Clinical remission at week 16 ($SF \leq 1.5$ or $AP \leq 1$, and both no worse from baseline)*

ns= non-significant

Acknowledgments

GWM research is supported by the National Institute for Health Research (NIHR), through the Biomedical Research Centre in Gastrointestinal and Liver Diseases at Nottingham University Hospitals NHS Trust and the University of Nottingham. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Guarantor of the article: Gordon W Moran

Author contributions: Gordon W Moran and Subrata Ghosh conceived the article; Jonathan R White and Frank Phillips wrote the article. All co-authors edited and approved the final version of the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Frolkis AD, Dykeman J, Negron ME, DeBruyn J, Jette N, Fiest KM, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology*. 2013 Nov;145(5):996-1006. PubMed PMID: 23896172.
2. Frolkis AD, Lipton DS, Fiest KM, Negron ME, Dykeman J, deBruyn J, et al. Cumulative incidence of second intestinal resection in Crohn's disease: a systematic review and meta-analysis of

- population-based studies. *The American journal of gastroenterology*. 2014 Nov;109(11):1739-48. PubMed PMID: 25331349.
3. Ma C, Moran GW, Benchimol EI, Targownik LE, Heitman SJ, Hubbard JN, et al. Surgical Rates for Crohn's Disease are Decreasing: A Population-Based Time Trend Analysis and Validation Study. *The American journal of gastroenterology*. 2017 Dec;112(12):1840-8. PubMed PMID: 29087396. Pubmed Central PMCID: 5729339.
 4. Burisch J, Jess T, Martinato M, Lakatos PL, EpiCom E. The burden of inflammatory bowel disease in Europe. *Journal of Crohn's & colitis*. 2013 May;7(4):322-37. PubMed PMID: 23395397.
 5. Timmer A, Patton PH, Chande N, McDonald JW, MacDonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *The Cochrane database of systematic reviews*. 2016 May 18(5):CD000478. PubMed PMID: 27192092.
 6. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *The New England journal of medicine*. 1997 Oct 09;337(15):1029-35. PubMed PMID: 9321530.
 7. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet*. 2002 May 04;359(9317):1541-9. PubMed PMID: 12047962.
 8. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *The New England journal of medicine*. 2005 Dec 08;353(23):2462-76. PubMed PMID: 16339095.
 9. Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology*. 2006 Feb;130(2):323-33; quiz 591. PubMed PMID: 16472588.
 10. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007 Jan;132(1):52-65. PubMed PMID: 17241859.
 11. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012 Feb;142(2):257-65 e1-3. PubMed PMID: 22062358.
 12. Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, et al. Certolizumab pegol for the treatment of Crohn's disease. *The New England journal of medicine*. 2007 Jul 19;357(3):228-38. PubMed PMID: 17634458.
 13. Rutgeerts P, Feagan BG, Marano CW, Padgett L, Strauss R, Johanns J, et al. Randomised clinical trial: a placebo-controlled study of intravenous golimumab induction therapy for ulcerative colitis. *Alimentary pharmacology & therapeutics*. 2015 Sep;42(5):504-14. PubMed PMID: 26119226. Pubmed Central PMCID: 4755132.
 14. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *The New England journal of medicine*. 2013 Aug 22;369(8):699-710. PubMed PMID: 23964932.
 15. Sandborn WJ, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. *Gastroenterology*. 2008 Oct;135(4):1130-41. PubMed PMID: 18706417.
 16. Talley NJ, Abreu MT, Achkar JP, Bernstein CN, Dubinsky MC, Hanauer SB, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. *The American journal of gastroenterology*. 2011 Apr;106 Suppl 1:S2-25; quiz S6. PubMed PMID: 21472012.
 17. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *The American journal of gastroenterology*. 2011 Apr;106(4):644-59, quiz 60. PubMed PMID: 21407183.
 18. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clinical and translational gastroenterology*. 2016 Jan 07;7:e135. PubMed PMID: 26741065. Pubmed Central PMCID: 4737871.

19. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Alimentary pharmacology & therapeutics*. 2011 May;33(9):987-95. PubMed PMID: 21366636.
20. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England journal of medicine*. 2001 Oct 11;345(15):1098-104. PubMed PMID: 11596589.
21. Lawrance IC, Radford-Smith GL, Bampton PA, Andrews JM, Tan PK, Croft A, et al. Serious infections in patients with inflammatory bowel disease receiving anti-tumor-necrosis-factor-alpha therapy: an Australian and New Zealand experience. *Journal of gastroenterology and hepatology*. 2010 Nov;25(11):1732-8. PubMed PMID: 21039834.
22. Rutgeerts P, Vermeire S, Van Assche G. Biological therapies for inflammatory bowel diseases. *Gastroenterology*. 2009 Apr;136(4):1182-97. PubMed PMID: 19249397.
23. Pedersen J, Coskun M, Soendergaard C, Salem M, Nielsen OH. Inflammatory pathways of importance for management of inflammatory bowel disease. *World journal of gastroenterology : WJG*. 2014 Jan 07;20(1):64-77. PubMed PMID: 24415859. Pubmed Central PMCID: 3886034.
24. Lobaton T, Vermeire S, Van Assche G, Rutgeerts P. Review article: anti-adhesion therapies for inflammatory bowel disease. *Alimentary pharmacology & therapeutics*. 2014 Mar;39(6):579-94. PubMed PMID: 24479980.
25. Barczyk M, Carracedo S, Gullberg D. Integrins. *Cell and tissue research*. 2010 Jan;339(1):269-80. PubMed PMID: 19693543. Pubmed Central PMCID: 2784866.
26. Saruta M, Papadakis KA. Lymphocyte homing antagonists in the treatment of inflammatory bowel diseases. *Gastroenterology clinics of North America*. 2014 Sep;43(3):581-601. PubMed PMID: 25110260.
27. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *The New England journal of medicine*. 2013 Aug 22;369(8):711-21. PubMed PMID: 23964933.
28. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, et al. Natalizumab induction and maintenance therapy for Crohn's disease. *The New England journal of medicine*. 2005 Nov 03;353(18):1912-25. PubMed PMID: 16267322.
29. Targan SR, Feagan BG, Fedorak RN, Lashner BA, Panaccione R, Present DH, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. *Gastroenterology*. 2007 May;132(5):1672-83. PubMed PMID: 17484865.
30. Vermeire S, O'Byrne S, Keir M, Williams M, Lu TT, Mansfield JC, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet*. 2014 Jul 26;384(9940):309-18. PubMed PMID: 24814090.
31. ClinicalTrials.gov. A Study of the Efficacy and Safety of Etrolizumab in Ulcerative Colitis Participants Who Are Refractory to or Intolerant of Tumor Necrosis Factor (TNF) Inhibitors 2017 [cited 2017 November 2017]. Available from: <https://clinicaltrials.gov/show/NCT02100696>.
32. ClinicalTrials.gov. A Study to Assess Whether Etrolizumab is a Safe and Effective Treatment for Participants With Moderately to Severely Active Crohn's Disease (CD) [cited 2017 November 2017]. Available from: <https://clinicaltrials.gov/show/NCT02394028>.
33. Sandborn WJ PJ, Jones J, Hassanali A, Jacob R, Sharafali Z, Oh YS, Tole S. Etrolizumab as induction therapy in moderate to severe Crohn's disease: Results from BERGAMOT Cohort 1. *United European Gastroenterology Week; 2017; Barcelona, Spain: United European Gastroenterology Journal; 2017*.
34. Sugiura T, Kageyama S, Andou A, Miyazawa T, Ejima C, Nakayama A, et al. Oral treatment with a novel small molecule alpha 4 integrin antagonist, AJM300, prevents the development of experimental colitis in mice. *Journal of Crohn's & colitis*. 2013 Dec;7(11):e533-42. PubMed PMID: 23623333.
35. Tidswell M, Pachynski R, Wu SW, Qiu SQ, Dunham E, Cochran N, et al. Structure-function analysis of the integrin beta 7 subunit: identification of domains involved in adhesion to MAdCAM-1. *Journal of immunology*. 1997 Aug 01;159(3):1497-505. PubMed PMID: 9233649.

36. Yoshimura N, Watanabe M, Motoya S, Tominaga K, Matsuoka K, Iwakiri R, et al. Safety and Efficacy of AJM300, an Oral Antagonist of α_4 Integrin, in Induction Therapy for Patients With Active Ulcerative Colitis. *Gastroenterology*. 2015 Dec;149(7):1775-83 e2. PubMed PMID: 26327130.
37. Van Assche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *The New England journal of medicine*. 2005 Jul 28;353(4):362-8. PubMed PMID: 15947080.
38. Urbano M, Guerrero M, Rosen H, Roberts E. Modulators of the Sphingosine 1-phosphate receptor 1. *Bioorganic & medicinal chemistry letters*. 2013 Dec 01;23(23):6377-89. PubMed PMID: 24125884. Pubmed Central PMCID: 3926431.
39. Marsolais D, Rosen H. Chemical modulators of sphingosine-1-phosphate receptors as barrier-oriented therapeutic molecules. *Nature reviews Drug discovery*. 2009 Apr;8(4):297-307. PubMed PMID: 19300460. Pubmed Central PMCID: 4455967.
40. Proia RL, Hla T. Emerging biology of sphingosine-1-phosphate: its role in pathogenesis and therapy. *The Journal of clinical investigation*. 2015 Apr;125(4):1379-87. PubMed PMID: 25831442. Pubmed Central PMCID: 4409021.
41. O'Sullivan C, Dev KK. The structure and function of the S1P1 receptor. *Trends in pharmacological sciences*. 2013 Jul;34(7):401-12. PubMed PMID: 23763867.
42. Sandborn WJ, Feagan BG, Wolf DC, D'Haens G, Vermeire S, Hanauer SB, et al. Ozanimod Induction and Maintenance Treatment for Ulcerative Colitis. *The New England journal of medicine*. 2016 May 05;374(18):1754-62. PubMed PMID: 27144850.
43. Sandborn WJ, D'Haens G, Hanauer S, Wolf DC, Vermeire S, Ghosh S, Li C, Penenberg D, Petersen A, Aranda R, Olson A. OP096 Safety and efficacy of long-term treatment with ozanimod, an oral S1P receptor modulator, in moderate to severe ulcerative colitis: TOUCHSTONE extension 2-year follow up. *United European Gastroenterology*; October 2017; Barcelona, Spain 2017. p. 40.
44. ClinicalTrials.gov. Efficacy and Safety Trial of RPC1063 for Moderate to Severe Crohn's Disease [cited 2017 11 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02531113>.
45. Feagan BG, D'Haens G, Levesque BG, Skolnick BE, Li C, Penenberg D, Aranda R, Olson A. OP009 Endoscopic and clinical efficacy demonstrated with oral ozanimod in moderately to severely active Crohn's Disease. *United European Gastroenterology*; October 2017; Barcelona, Spain 2017. p. 5.
46. ClinicalTrials.gov. A Phase 3, Multicenter, Open-Label Extension Trial of Oral RPC1063 as Therapy for Moderate to Severe Ulcerative Colitis [cited 2017 11 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02531126>.
47. ClinicalTrials.gov. A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Oral RPC1063 as Induction and Maintenance Therapy for Moderate to Severe Ulcerative Colitis [cited 2017 11 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02435992>.
48. Peyrin-Biroulet L, Christopher R, Behan D, Lassen C. Modulation of sphingosine-1-phosphate in inflammatory bowel disease. *Autoimmunity reviews*. 2017 May;16(5):495-503. PubMed PMID: 28279838.
49. ClinicalTrials.gov. Safety and Efficacy of APD334 in Patients With Ulcerative Colitis [cited 2017 11 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02447302>.
50. ClinicalTrials.gov. Extension Study of APD334-003 in Patients With Moderately to Severely Active Ulcerative Colitis [cited 2017 11 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02536404>.
51. ClinicalTrials.gov. A Phase II, Open-label, Multicentre Study to Evaluate the Long-term Safety and Efficacy of MT-1303 in Subjects With Moderate to Severe Active Crohn's Disease Who Have Completed the MT 1303-E13 Study [cited 2017 11 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02389790>.
52. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochemical pharmacology*. 2012 Jun 15;83(12):1583-90. PubMed PMID: 22257911.

53. Danese D NM, Kopon A, Zakko S, Simmons T, Fogel R, Maccarone J, Zhan X, Usiskin K, Chitkara D. OP006 Apremilast for active ulcerative colitis: a phase 2, randomised, double-blind, placebo-controlled induction study ECCO; 16 February 2018; Vienna, Austria: Journal of Crohn's Colitis; 2018. p. S004–S5.
54. ClinicalTrials.gov. Efficacy and Safety Study of Apremilast to Treat Active Ulcerative Colitis (UC) 2018 [cited 2018 27th February 2018]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02289417>.
55. Waetzig GH, Seegert D, Rosenstiel P, Nikolaus S, Schreiber S. p38 mitogen-activated protein kinase is activated and linked to TNF-alpha signaling in inflammatory bowel disease. *Journal of immunology*. 2002 May 15;168(10):5342-51. PubMed PMID: 11994493.
56. Murthy S, Flanagan A, Coppola D, Buelow R. RDP58, a locally active TNF inhibitor, is effective in the dextran sulphate mouse model of chronic colitis. *Inflammation research : official journal of the European Histamine Research Society* [et al]. 2002 Nov;51(11):522-31. PubMed PMID: 12540016.
57. Travis S, Yap LM, Hawkey C, Warren B, Lazarov M, Fong T, et al. RDP58 is a novel and potentially effective oral therapy for ulcerative colitis. *Inflammatory bowel diseases*. 2005 Aug;11(8):713-9. PubMed PMID: 16043985.
58. Braun A, Treede I, Gotthardt D, Tietje A, Zahn A, Ruhwald R, et al. Alterations of phospholipid concentration and species composition of the intestinal mucus barrier in ulcerative colitis: a clue to pathogenesis. *Inflammatory bowel diseases*. 2009 Nov;15(11):1705-20. PubMed PMID: 19504612.
59. Podolsky DK. Inflammatory bowel disease. *The New England journal of medicine*. 2002 Aug 08;347(6):417-29. PubMed PMID: 12167685.
60. Karner M, Kocjan A, Stein J, Schreiber S, von Boyen G, Uebel P, et al. First multicenter study of modified release phosphatidylcholine "LT-02" in ulcerative colitis: a randomized, placebo-controlled trial in mesalazine-refractory courses. *The American journal of gastroenterology*. 2014 Jul;109(7):1041-51. PubMed PMID: 24796768. Pubmed Central PMCID: 4085478.
61. ClinicalTrials.gov. A Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of a 12-week Add-on Treatment With LT-02 vs. Placebo in Subjects With Ulcerative Colitis Refractory to Standard Treatment With Mesalamine [cited 2017 25 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02849951>.
62. ClinicalTrials.gov. Randomized, Double-blind, Double-dummy, Placebo-controlled, Phase III Clinical Trial on the Efficacy and Safety of a 12-weeks add-on Treatment With LT 02 vs. Placebo in Patients With Ulcerative Colitis Refractory to Standard Treatment With Mesalamine [cited 2017 25 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02142725>.
63. ClinicalTrials.gov. Randomized, Double-blind, Double-dummy, Placebo-controlled, Phase III Clinical Trial on the Efficacy and Safety of a 48-weeks Treatment With Gastro-resistant Phosphatidylcholine (LT-02) Versus Placebo Versus Mesalamine for Maintenance of Remission in Patients With Ulcerative Colitis [cited 2017 25 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02280629>.
64. Kim MH, Kang SG, Park JH, Yanagisawa M, Kim CH. Short-chain fatty acids activate GPR41 and GPR43 on intestinal epithelial cells to promote inflammatory responses in mice. *Gastroenterology*. 2013 Aug;145(2):396-406 e1-10. PubMed PMID: 23665276.
65. Namour F, Galien R, Van Kaem T, Van der Aa A, Vanhoutte F, Beets J, et al. Safety, pharmacokinetics and pharmacodynamics of GLPG0974, a potent and selective FFA2 antagonist, in healthy male subjects. *British journal of clinical pharmacology*. 2016 Jul;82(1):139-48. PubMed PMID: 26852904. Pubmed Central PMCID: 4917808.
66. ClinicalTrials.gov. Exploratory, Phase II, Randomized, Double-blind, Placebo-controlled, Proof-of-Concept Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics and Pharmacodynamics of GLPG0974 in Subjects With Mild to Moderate Ulcerative Colitis [cited 2017 25 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01829321>.

67. ClinicalTrials.gov. A Multicenter Open-label Extension Study to Assess the Safety and Tolerability of LYC-30937-EC in Subjects With Active Ulcerative Colitis. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02764229>.
68. ClinicalTrials.gov. A Randomized, Double-Blind, Placebo-Controlled Parallel Group Study to Assess the Efficacy and Safety of Induction Therapy With LYC-30937-EC in Subjects With Active Ulcerative Colitis [cited 14 August 2017]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02762500>.
69. ClinicalTrials.gov. A Phase 2a, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety/Tolerability and Efficacy of TOP1288 200 mg Rectal Solution Once Daily for 4 Weeks in Symptomatic Ulcerative Colitis Patients With Moderate to Severe Disease Activity [cited 2017 24 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02888379>.
70. ClinicalTrials.gov. A Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of TOP1288 Oral Single Ascending and Multiple Doses in Healthy Volunteers [cited 2017 25 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT03071081>.
71. ClinicalTrials.gov. A Multicentre, Randomised, Double-blind (Sponsor Unblinded), Placebo-controlled Study With Open Label Extension to Investigate the Safety and Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of GSK2982772 in Subjects With Active Ulcerative Colitis [cited 2017 25 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02903966>.
72. Lewis JD, Lichtenstein GR, Deren JJ, Sands BE, Hanauer SB, Katz JA, et al. Rosiglitazone for active ulcerative colitis: a randomized placebo-controlled trial. *Gastroenterology*. 2008 Mar;134(3):688-95. PubMed PMID: 18325386. Pubmed Central PMCID: 2276587.
73. clinicalTrials.gov. A Randomized, Double-Blind, 12-Week, Placebo-Controlled Study Followed by a 12-Week Extension Phase Without Placebo to Evaluate the Efficacy and Safety of Oral VB-201 in Subjects With Mild to Moderate Ulcerative Colitis [cited 2017 12 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01839214>.
74. Harris MS, Hartman D, Lemos BR, Erlich EC, Spence S, Kennedy S, et al. AVX-470, an Orally Delivered Anti-Tumour Necrosis Factor Antibody for Treatment of Active Ulcerative Colitis: Results of a First-in-Human Trial. *Journal of Crohn's & colitis*. 2016 Jun;10(6):631-40. PubMed PMID: 26822613.
75. Kolb-Sobieraj C, Gupta S, Weinstock-Guttman B. Laquinimod therapy in multiple sclerosis: a comprehensive review. *Neurology and therapy*. 2014 Jun;3(1):29-39. PubMed PMID: 26000222. Pubmed Central PMCID: 4381916.
76. Comi G, Jeffery D, Kappos L, Montalban X, Boyko A, Rocca MA, et al. Placebo-controlled trial of oral laquinimod for multiple sclerosis. *The New England journal of medicine*. 2012 Mar 15;366(11):1000-9. PubMed PMID: 22417253.
77. Wild EJ, Tabrizi SJ. Targets for future clinical trials in Huntington's disease: what's in the pipeline? *Movement disorders : official journal of the Movement Disorder Society*. 2014 Sep 15;29(11):1434-45. PubMed PMID: 25155142. Pubmed Central PMCID: 4265300.
78. Rovin BH, Parikh SV. Lupus nephritis: the evolving role of novel therapeutics. *American journal of kidney diseases : the official journal of the National Kidney Foundation*. 2014 Apr;63(4):677-90. PubMed PMID: 24411715. Pubmed Central PMCID: 4159074.
79. Kieseier BC. Defining a role for laquinimod in multiple sclerosis. *Therapeutic advances in neurological disorders*. 2014 Jul;7(4):195-205. PubMed PMID: 25002907. Pubmed Central PMCID: 4082303.
80. Bjork P, Bjork A, Vogl T, Stenstrom M, Liberg D, Olsson A, et al. Identification of human S100A9 as a novel target for treatment of autoimmune disease via binding to quinoline-3-carboxamides. *PLoS biology*. 2009 Apr 28;7(4):e97. PubMed PMID: 19402754. Pubmed Central PMCID: 2671563 which is developing quinolines for commercial purposes. FI has a research grant from Active Biotech.
81. Toubi E, Nussbaum S, Staun-Ram E, Snir A, Melamed D, Hayardeny L, et al. Laquinimod modulates B cells and their regulatory effects on T cells in multiple sclerosis. *Journal of neuroimmunology*. 2012 Oct 15;251(1-2):45-54. PubMed PMID: 22846497.

82. Wegner C, Stadelmann C, Pfortner R, Raymond E, Feigelson S, Alon R, et al. Laquinimod interferes with migratory capacity of T cells and reduces IL-17 levels, inflammatory demyelination and acute axonal damage in mice with experimental autoimmune encephalomyelitis. *Journal of neuroimmunology*. 2010 Oct 08;227(1-2):133-43. PubMed PMID: 20684995.
83. Jolivel V, Luessi F, Masri J, Kraus SH, Hubo M, Poisa-Beiro L, et al. Modulation of dendritic cell properties by laquinimod as a mechanism for modulating multiple sclerosis. *Brain : a journal of neurology*. 2013 Apr;136(Pt 4):1048-66. PubMed PMID: 23518712.
84. D'Haens G, Sandborn WJ, Colombel JF, Rutgeerts P, Brown K, Barkay H, et al. A phase II study of laquinimod in Crohn's disease. *Gut*. 2015 Aug;64(8):1227-35. PubMed PMID: 25281416. Pubmed Central PMCID: 4515993.
85. D'Haens GR SW, Colombel JW, Mimrod D, Spiegelstein O, Brown K, Feagan BG. Su1084 Pharmacokinetics of Laquinimod in Patients With Active Moderate to Severe Crohn's Disease. *DDW; May 2014. Gastroenterology*2014. p. S-368.
86. Monteleone G, Kumberova A, Croft NM, McKenzie C, Steer HW, MacDonald TT. Blocking Smad7 restores TGF-beta1 signaling in chronic inflammatory bowel disease. *The Journal of clinical investigation*. 2001 Aug;108(4):601-9. PubMed PMID: 11518734. Pubmed Central PMCID: 209401.
87. Olivera P, Danese S, Peyrin-Biroulet L. Next generation of small molecules in inflammatory bowel disease. *Gut*. 2017 Feb;66(2):199-209. PubMed PMID: 27856614.
88. Mantel PY, Schmidt-Weber CB. Transforming growth factor-beta: recent advances on its role in immune tolerance. *Methods in molecular biology*. 2011;677:303-38. PubMed PMID: 20941619.
89. Monteleone G, Neurath MF, Ardizzone S, Di Sabatino A, Fantini MC, Castiglione F, et al. Mongersen, an oral SMAD7 antisense oligonucleotide, and Crohn's disease. *The New England journal of medicine*. 2015 Mar 19;372(12):1104-13. PubMed PMID: 25785968.
90. Monteleone G, Di Sabatino A, Ardizzone S, Pallone F, Usiskin K, Zhan X, et al. Impact of patient characteristics on the clinical efficacy of mongersen (GED-0301), an oral Smad7 antisense oligonucleotide, in active Crohn's disease. *Alimentary pharmacology & therapeutics*. 2016 Mar;43(6):717-24. PubMed PMID: 26766141. Pubmed Central PMCID: 4849204.
91. Mosli MH, Zou G, Garg SK, Feagan SG, MacDonald JK, Chande N, et al. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. *The American journal of gastroenterology*. 2015 Jun;110(6):802-19; quiz 20. PubMed PMID: 25964225.
92. ClinicalTrials.gov. A Phase 2, Open-Label, Multicenter Study to Explore the Efficacy and Safety of MONGERSON (GED-0301) in Subjects With Active Ulcerative Colitis [cited 2017 11 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02601300>.
93. Boland BS, Sandborn WJ, Chang JT. Update on Janus kinase antagonists in inflammatory bowel disease. *Gastroenterology clinics of North America*. 2014 Sep;43(3):603-17. PubMed PMID: 25110261. Pubmed Central PMCID: 4129380.
94. Coskun M, Salem M, Pedersen J, Nielsen OH. Involvement of JAK/STAT signaling in the pathogenesis of inflammatory bowel disease. *Pharmacological research*. 2013 Oct;76:1-8. PubMed PMID: 23827161.
95. Changelian PS, Moshinsky D, Kuhn CF, Flanagan ME, Munchhof MJ, Harris TM, et al. The specificity of JAK3 kinase inhibitors. *Blood*. 2008 Feb 15;111(4):2155-7. PubMed PMID: 18094329.
96. Danese S, Grisham M, Hodge J, Telliez JB. JAK inhibition using tofacitinib for inflammatory bowel disease treatment: a hub for multiple inflammatory cytokines. *American journal of physiology Gastrointestinal and liver physiology*. 2016 Feb 01;310(3):G155-62. PubMed PMID: 26608188. Pubmed Central PMCID: 4971816.
97. Archer TP, Moran GW, Ghosh S. Tofacitinib in ulcerative colitis. *Immunotherapy*. 2016 May;8(5):495-502. PubMed PMID: 27140405.
98. Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis and rheumatism*. 2009 Jul;60(7):1895-905. PubMed PMID: 19565475.

99. Papp KA, Menter MA, Abe M, Elewski B, Feldman SR, Gottlieb AB, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. *The British journal of dermatology*. 2015 Oct;173(4):949-61. PubMed PMID: 26149717.
100. Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. *The New England journal of medicine*. 2012 Aug 16;367(7):616-24. PubMed PMID: 22894574.
101. Panes J, Su C, Bushmakina AG, Cappelleri JC, Mamolo C, Healey P. Randomized trial of tofacitinib in active ulcerative colitis: analysis of efficacy based on patient-reported outcomes. *BMC gastroenterology*. 2015 Feb 05;15:14. PubMed PMID: 25651782. Pubmed Central PMCID: 4323227.
102. Sandborn WJ, Panes J, Zhang H, Yu D, Niezychowski W, Su C. Correlation Between Concentrations of Fecal Calprotectin and Outcomes of Patients With Ulcerative Colitis in a Phase 2 Trial. *Gastroenterology*. 2016 Jan;150(1):96-102. PubMed PMID: 26376350.
103. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *The New England journal of medicine*. 2017 May 04;376(18):1723-36. PubMed PMID: 28467869.
104. Lichtenstein GR LE, Bloom S, Lawendy N, Friedman G, Zhang H, Wang W, Thorpe AJ, Nduaka C, Su C. OP095 Tofacitinib, an oral Janus Kinase Inhibitor, in the treatment of ulcerative colitis: open-label long-term extension study. *United European Gastroenterology*; October 2017; Barcelona, Spain 2017. p. 39-40.
105. ClinicalTrials.gov. A Phase 1a, Double-Blinded, Randomized, Placebo Controlled, Single Ascending Dose (SAD) Study to Evaluate the Safety, Tolerability, and Systemic Exposure of TD-3504 in Healthy Subjects and Subjects With Ulcerative Colitis (UC) [cited 2017 14 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT03103412>.
106. ClinicalTrials.gov. This study is an open label, long-term extension study for subjects with moderate to severe ulcerative colitis designed to evaluate long term therapy of CP-690,550 [cited 2017 20 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01470612>.
107. Sandborn WJ, Ghosh S, Panes J, Vranic I, Wang W, Niezychowski W, et al. A phase 2 study of tofacitinib, an oral Janus kinase inhibitor, in patients with Crohn's disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2014 Sep;12(9):1485-93 e2. PubMed PMID: 24480677.
108. Panés J SW, Schreiber S, Sands BE, Vermeire S, Chan G, Moscariello M, Wang W, Niezychowski W, Marren A, Healey PJ, Maller E. 855 Efficacy and Safety of Tofacitinib for Oral Induction Therapy in Patients With Moderate to Severe Crohn's Disease: Results of a Phase 2B Randomized Placebo-Controlled Trial [Abstract]. *DDW*; April 2016: *Gastroenterology*; 2016. p. S182–S3.
109. Panes J, Sandborn WJ, Schreiber S, Sands BE, Vermeire S, D'Haens G, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. *Gut*. 2017 Jun;66(6):1049-59. PubMed PMID: 28209624. Pubmed Central PMCID: 5532457.
110. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *The New England journal of medicine*. 2010 Apr 15;362(15):1383-95. PubMed PMID: 20393175.
111. Vermeire S, Schreiber S, Petryka R, Kuehbach T, Hebuterne X, Roblin X, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. *Lancet*. 2017 Jan 21;389(10066):266-75. PubMed PMID: 27988142.
112. Vermeire S VDAA, Jamoul C, Tasset C, Harrison P, D'Haens GR. OP005 Effect of disease duration and location on clinical remission in Crohn's disease patients treated with filgotinib, a selective JAK1 inhibitor: Post-hoc analysis from the phase 2 Fitzroy study. *United European Gastroenterology* October 2017; Barcelona, Spain 2017. p. 2, 3.

113. ClinicalTrials.gov. A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects With Crohn's Disease [cited 2017 14 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02914600>.
114. ClinicalTrials.gov. Combined Phase 3, Double-blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects With Moderately to Severely Active Crohn's Disease [cited 2017 14 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02914561>.
115. ClinicalTrials.gov. A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects With Ulcerative Colitis [cited 2017 14 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02914535>.
116. ClinicalTrials.gov. Combined Phase 2b/3, Double-Blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects With Moderately to Severely Active Ulcerative Colitis [cited 2017 14 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02914522>.
117. Sanborn WJ FB, Panes J, D'Haens G, Colombel J, Zhou Q, Huang B, Enejosa JV, Pangan AL, Lacerda AP. OP007 Safety and efficacy of Upadacitinib (ABT-494), an oral JAK1 inhibitor, as induction therapy in patients with Crohn's Disease: Results from CELEST. United European Gastroenterology Barcelona, Spain 2017. p. 3,4.
118. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of ABT-494 for the Induction of Symptomatic and Endoscopic Remission in Subjects With Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or Are Intolerant to Immunomodulators or Anti-TNF Therapy 2017 [11th August 2017]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02365649>.
119. Schreiber S P-BL, Boland B, Higgins PD, Armuzzi A, Terdiman J, Zhou W, Alperovich G, Cataldi F, Goteti S, Lacerda AP. OP022 Rapidity of clinical and laboratory improvements following upadacitinib induction treatment: data from the CELEST study ECCO; 16th February 2018; Vienna, Austria: Journal of Crohn's and Colitis; 2018. p. S015.
120. A Study to Evaluate the Safety and Efficacy of ABT-494 for Induction and Maintenance Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis 2017 [11th August 2017]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02819635>.
121. ClinicalTrials.gov. A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group, Dose-response Study Evaluating the Efficacy and Safety of JNJ-54781532 in Subjects With Moderately to Severely Active Ulcerative Colitis [cited 2017 14 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT01959282>.
122. ClinicalTrials.gov. A Phase 1b Multi-Center, Randomized, Double-Blind, Multi-Dose, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Plasma Exposure of TD-1473 in Subjects With Moderately-to-Severely Active Ulcerative Colitis [cited 2017 14 August]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02818686>.
123. Leban J, Kralik M, Mies J, Gassen M, Tentschert K, Baumgartner R. SAR, species specificity, and cellular activity of cyclopentene dicarboxylic acid amides as DHODH inhibitors. Bioorganic & medicinal chemistry letters. 2005 Nov 01;15(21):4854-7. PubMed PMID: 16143532.
124. Herrlinger KR, Diculescu M, Fellermann K, Hartmann H, Howaldt S, Nikolov R, et al. Efficacy, safety and tolerability of vidofludimus in patients with inflammatory bowel disease: the ENTRANCE study. Journal of Crohn's & colitis. 2013 Sep;7(8):636-43. PubMed PMID: 23078909.
125. Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PD, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut. 2012 Dec;61(12):1693-700. PubMed PMID: 22595313. Pubmed Central PMCID: 4902107.
126. Asadullah K, Sterry W, Volk HD. Interleukin-10 therapy--review of a new approach. Pharmacological reviews. 2003 Jun;55(2):241-69. PubMed PMID: 12773629.

127. Kakkar A, Wasan SK, Farraye FA. Targeting mucosal healing in Crohn's disease. *Gastroenterology & hepatology*. 2011 Jun;7(6):374-80. PubMed PMID: 21869869. Pubmed Central PMCID: 3151410.
128. Kaplan GG, Seow CH, Ghosh S, Molodecky N, Rezaie A, Moran GW, et al. Decreasing colectomy rates for ulcerative colitis: a population-based time trend study. *The American journal of gastroenterology*. 2012 Dec;107(12):1879-87. PubMed PMID: 23165448.